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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/472,232	12/27/99	DUMAS J	BAYER-9-C1

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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	5

DATE MAILED: 02/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/472,232	Dumas et al.
Examiner	**Group Art Unit**
Deepak Rao	1624

[X] Responsive to communication(s) filed on *Dec 27, 1999*

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) *1-25* is/are pending in the applicat

Of the above, claim(s) *11-14* is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) *1-10 and 15-25* is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[X] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____ .

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[X] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[X] Notice of References Cited, PTO-892

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-25 are pending in this application.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10 and 15-25, drawn to compounds of formula I wherein A is pyrazolyl, corresponding composition and method of use, classified in class 548, subclass 371.7.

II. Claims 1-8, 11-12 and 15-25, drawn to compounds of formula I wherein A is thienyl, corresponding composition and method of use, classified in class 549, subclass 29+.

III. Claims 1-8 and 13-25, drawn to compounds of formula I wherein A is furyl, corresponding composition and method of use, classified in class 549, subclass 429+.

The inventions are distinct, each from the other because of the following reasons:

The compounds of Groups I-III are drawn to structurally dissimilar compounds. They are made independently and used independently. They would be expected to raise different issues of patentability if a compound of Group I, consisting of a pyrazolyl compound is anticipated, the anticipatory reference would not necessarily render obvious compounds of groups II or III or

vice-versa. They are not art recognized equivalents, they are classified separately and require separate burdensome searches in the literature and patent documents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Richard Traverso on February 8, 2001 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10 and 15-25. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

The first paragraph in the specification indicates that the instant application is a 'continuation of S.No. 09/303,621 filed December 22, 1998, which is a continuation-in-part of S.No. 60/126,439, which was converted from 08/996,184'. First, an application claiming the

benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation-in-part" of the provisional application, see MPEP§ 201.08. Further, the serial number of the provisional application provided in the first paragraph of the specification is different from the serial number (60/135,502) provided in the Declaration. Appropriate amendment of the priority data is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). See page 3, the Post Office Address of inventor 209 has been altered.

The inventor (203) Timothy Lowinger has signed at two places (203 and 210), see page 4.

Specification

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class.

While the instant abstract describes a class of the compounds, it does not contain the exemplification of the structural features of the compounds. Since the claims are drawn to compounds of a specific formula, inclusion of such formula would be considered illustrative of the members of the class of the compounds.

Complete revision of the content of the abstract is required on a separate sheet.

Claim Rejections

Claims 1-8 and 15-25 are rejected as being drawn to an Improper Markush Group(s). *In re Harnisch*, 206 USPQ 300. The claimed compounds, the composition containing the compounds and the methods employing the compounds, present a variable core and, thus, the Markush groups represented by the term A having variably different definitions, render the claims clearly improper. It is considered that a Markush-type claim encompassing such species is directed to multiple independent and patentably distinct inventions when the species are so unrelated and diverse that a reference anticipating the claims with regard to one of the species will not render obvious under 35 U.S.C. 103(a) with respect to another member. Furthermore, in this regard, lack of a common nucleus or core is evidentiary of independent and distinct inventions and also from the variably diverse definitions of A. Each species can be considered to be patentably distinct from the other on the basis of its properties.

Deletion of non elected subject matter obviates this rejection.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of carcinoma of colon, does not reasonably provide enablement for all other diseases mediated by raf kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to the treatment of 'disease mediated by raf kinase' and according to the specification, the compounds are useful in the treatment of tumors and/or cancerous cell growth mediated by raf kinase, see specification page 2, lines 5-17. Further, the specification discloses several types of cancers, e.g., solid cancers, myeloid disorders, adenomas. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Further, no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004).

Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers and/or diseases mediated by raf kinase in general.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating hyperproliferative diseases, which include cancers and noncancerous diseases.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of cancers.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders embraced by the instant claims nor there are doses given for the treatment of the disorders recited. The specification provides assays (see pages 33-35) to test the compounds *in vitro* and discloses that the compounds exhibit raf kinase inhibitory properties. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests. *In vivo* test procedures are provided for the cancers of the colon in mice (see page 35), however, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims. 6) The breadth of the claims: The instant claims embrace the treatment of all diseases mediated by raf kinase. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). 7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim 1 is drawn to "A compound of formula I **and** pharmaceutically acceptable salts thereof", which is confusing because it is not clear if a compound **or** its salt, etc. is claimed; or a mixture of a compound and its salt is claimed.

2. In claim 3, line 6, the recitation "substituted or **unsubstituted by halogen**" is not clear. Rearranging the terms unsubstituted and substituted to recite --unsubstituted or substituted by halogen-- would make the phrase clear. Same discrepancy appears in claim 4, lines 7-8, claim 5, lines 2, 5-7 (three occurrences), claim 17, line 6, claim 18, lines 7-8 and claim 19, lines 2, 5-7 (three occurrences).

3. Claim 4 recites the limitation "B is $-Q(X_n)-(-Y-Q^1-)_s-Z_{n1}$" in lines 1-2. There is insufficient antecedent basis for this limitation in claim 1 on which claim 4 is dependent. Claim 1 defines B to be aryl or heteroaryl moiety, which can be further substituted by X_n wherein n is 0-3 and X definition includes -Y-Ar, wherein Ar is a 5- or 6-membered aromatic group. The instant definition of B in claim 4 contains a first six membered aromatic ring moiety (Q) which has a X_n substituent and a Z_{n1} substituent (when s is 0) or a $(Y-Q^1-)-Z_{n1}$ substituent (when s is 1) wherein Q^1 is a mono or bicyclic aromatic group of 3-10 carbon

atoms. The definition of B in claim 4 is broader than that is provided in claim 1. Same discrepancy appears in claim 18, which lacks antecedent basis from claim 15.

4. Claim 4, line 10, the recitation "unsubstituted or **un**substituted by" is not clear. Repetition of 'unsubstituted' is confusing. Same discrepancy appears in claim 18 at line 10.

5. In claim 5, line 11, the recitation "R^6 and R^7 can be substituted by halogen **or** up to per-halosubstitution" is unclear. The presence of the term "or" is confusing. Claim 19 also contains the same recitation, see line 11.

6. In claim 15, line 4, following "wherein A is a heteroaryl selected from the group consisting of", the structures are not present. The structures present at line 8 should be inserted at line 5.

7. In claim 15, there is no recitation of the 'effective amount' of the compound. The specification discloses that the treatment of the diseases mediated by raf kinase is by inhibition of raf kinase, and therefore, the claim should contain the appropriate recitation of the effective amount.

8. In claim 23, the recitation "effective to inhibit raf" appears to be incomplete. The specification discloses that the enzyme is 'raf kinase' and therefore, the enzyme should be recited as disclosed. Further, if claim 15 is amended to include the recitation of the 'effective amount', claim 23 would be a substantial duplicate of claim 15. See MPEP § 706.03(k) regarding duplicate claims.

9. Claims 24-25, drawn to pharmaceutical compositions, do not recite 'an effective amount'.

The claims not particularly addressed above are included because they are dependent claims do not resolve the above issues.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10 and 24-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Regan et al., U.S. Patent No. 6,080,763. The instantly claimed compounds read on the compounds of the reference, see the examples, particularly Example 3 and the compounds listed in Table 1, col. 35-38, wherein the Het group is A (pyrazolyl).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-10 and 24-25 are rejected under 35 U.S.C. 102(e) as anticipated by (see above) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Regan et al., U.S. Patent No. 6,080,763. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula (I) in col. 6 wherein the heteroaryl ring represented by ABDEG is a pyrazolyl ring as shown in the examples. The compounds are taught to be useful as pharmaceutical therapeutic agents, see the abstract. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have

been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

2. Claims 1-5, 7-10 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creswell et al., U.S. Patent No. 5,162,360. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See Formula I in col. 2 wherein Het ring is a pyrazolyl ring as shown in col. 3, structure (7), R_{10} is alkyl and R_{11} is 2-pyridyl and see Example 24. The compounds are taught to be useful as pharmaceutical therapeutic agents, see col. 5, starting at line 55. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed on July 21, 2000 and a copy is enclosed herewith. References BP and BQ are crossed off from the list because they are not considered to be relevant to the instantly claimed invention. References ES-EZ have been considered, however, have been crossed off from the list because they are not individual publications but a compilation of several publications which are part of an online electronic database search. See MPEP § 609, 707.05 regarding proper format of citing electronic documents.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
February 13, 2001